ON LINE FIGURES

High Frequency Autonomic Modulation: a new model for analysis of autonomic cardiac control

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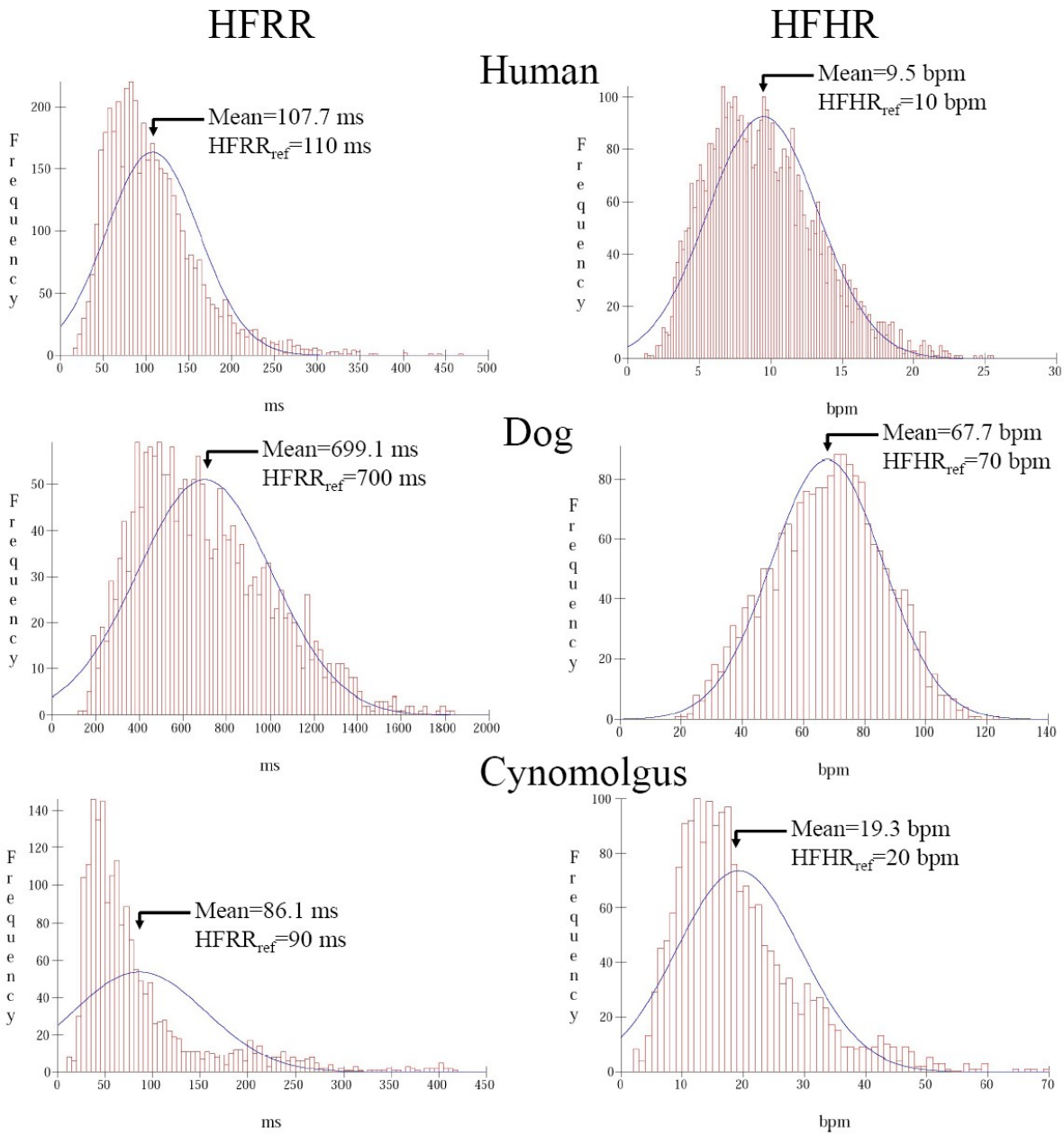

Figure 1. Histograms of distribution of discrete mean values (i.e. 1 value per hour) over the entire circadian cycle (i.e. 24 values per animal/subject) of HFRR and HFHR oscillations in healthy human subjects (n=200), beagle dogs (n=82) and cynomolgus monkeys (n=77). Animals were recorded in baseline conditions (treatment free recording period) for 24 hours by telemetry. Solid blue line: normal curve. $HFRR_{ref}$ and $HFHR_{ref}$ are rounded values of the mean values calculated from all individual values of the entire distribution in each species.

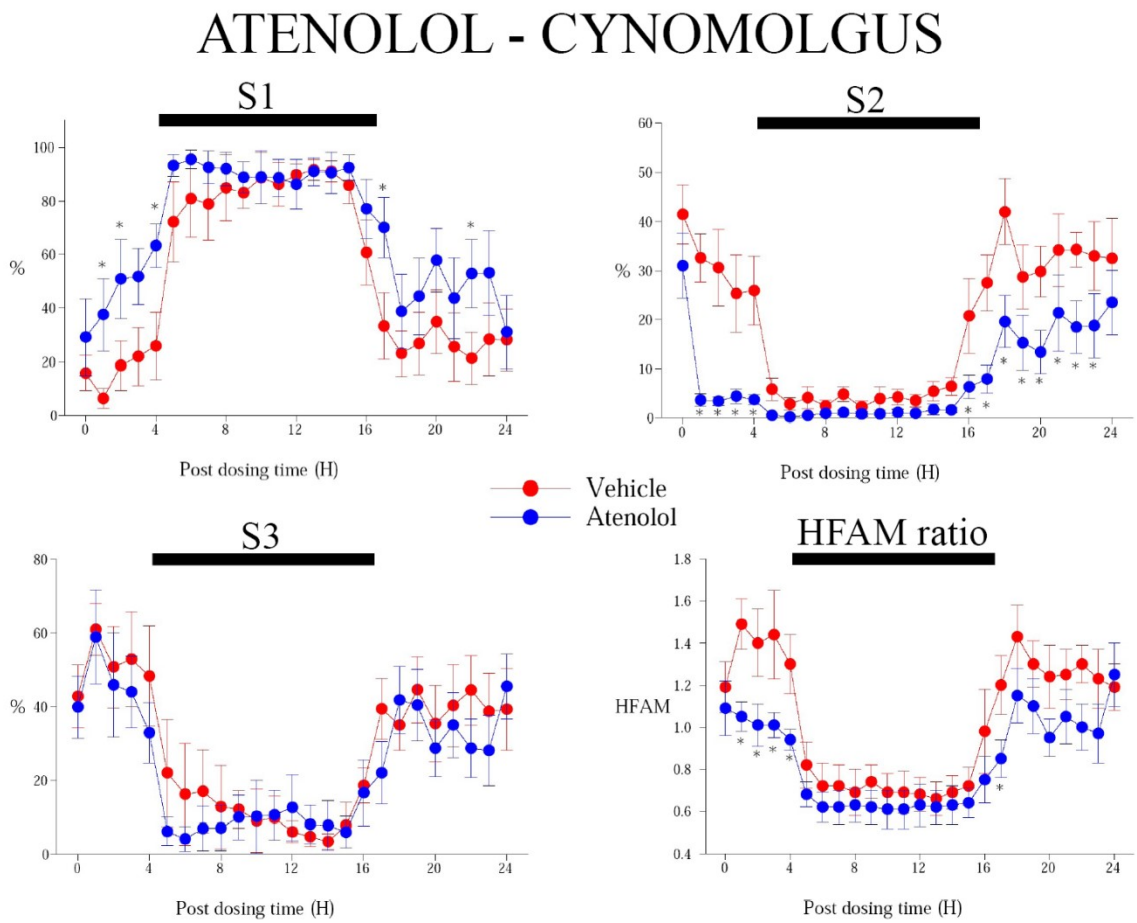

Figure 2. Effect of atenolol (1mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in cynomolgus monkeys. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05 when compared to vehicle).

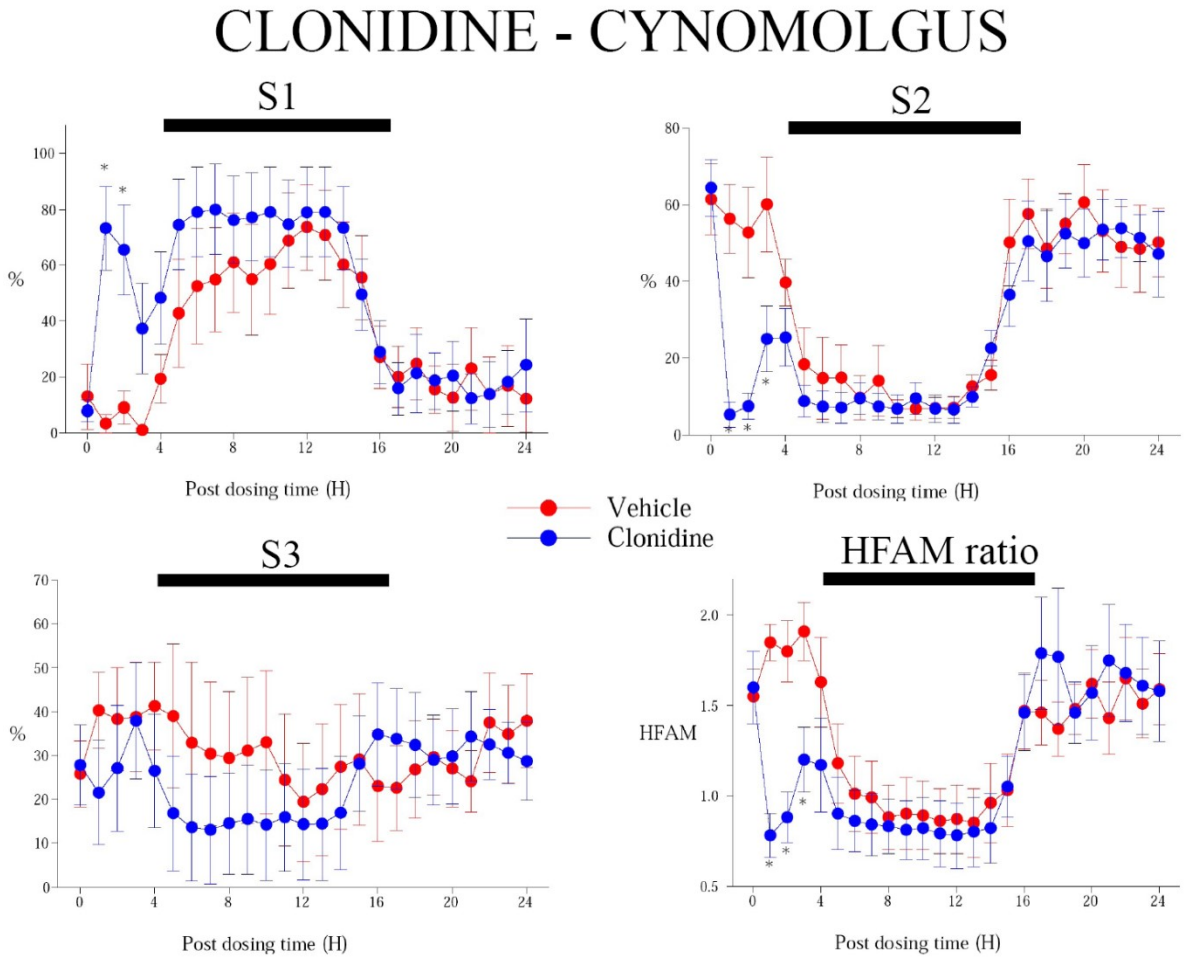

Figure 3. Effect of clonidine (0.1mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in cynomolgus monkeys. Black line: Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

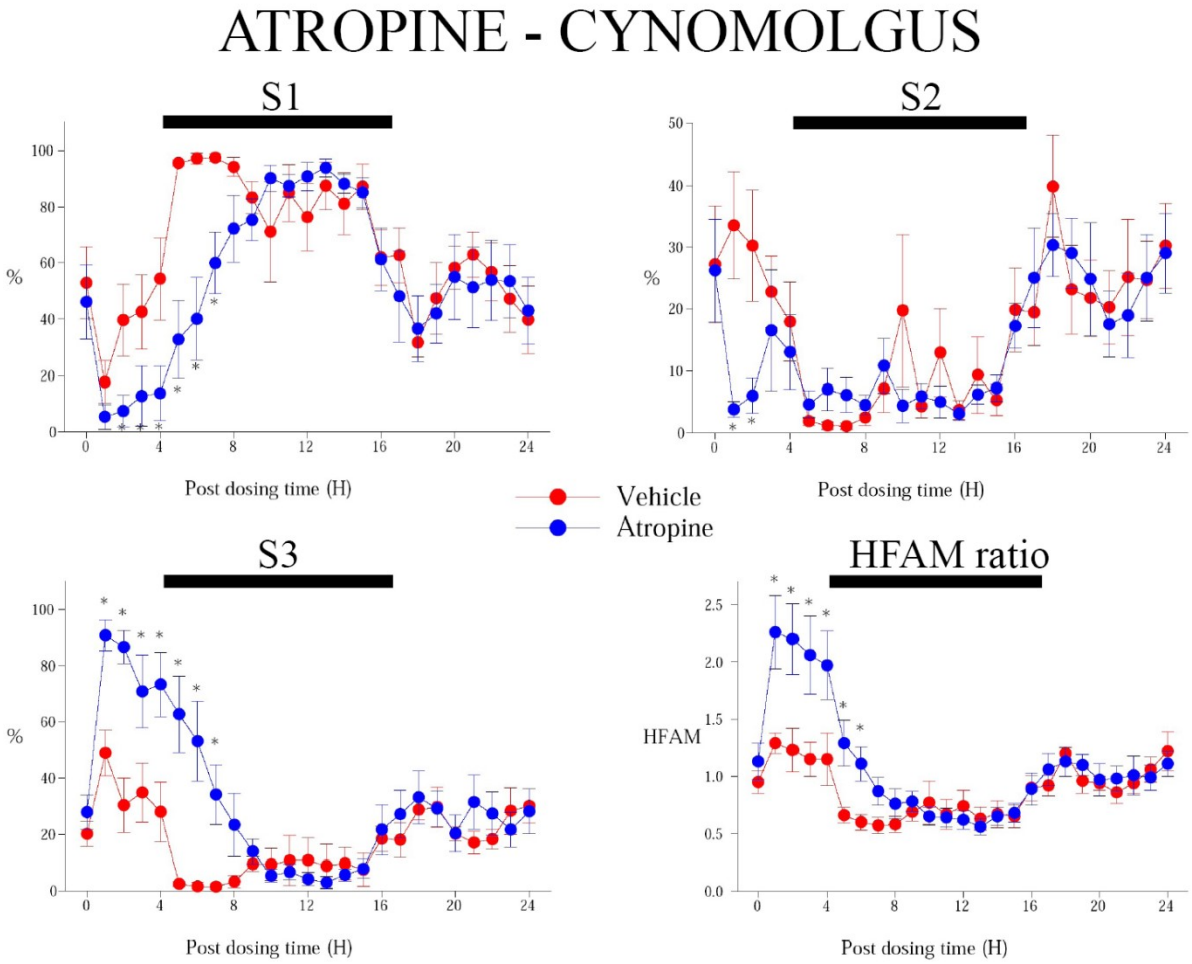

Figure 4. Effect of atropine sulphate (1 mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in cynomolgus monkeys. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

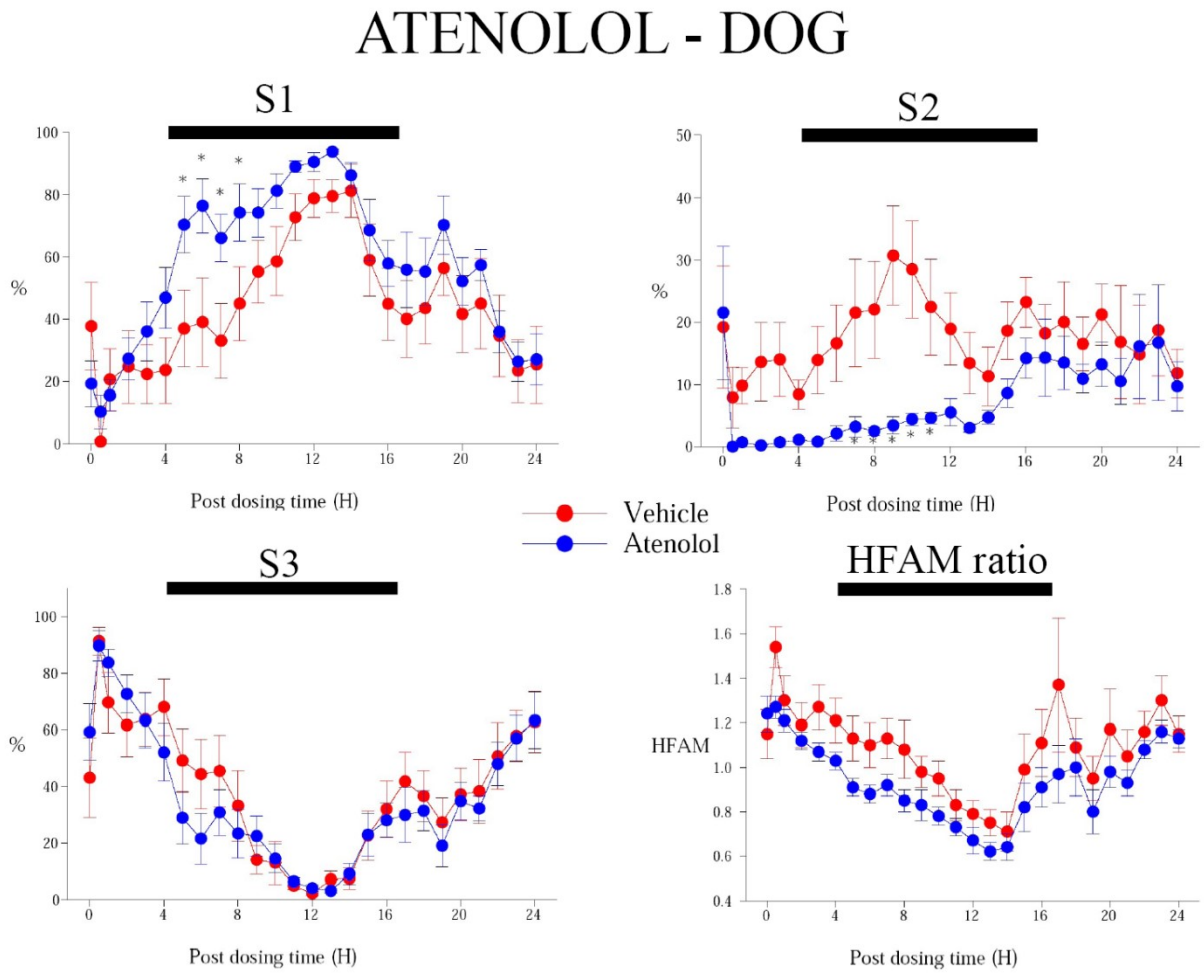

Figure 5. Effect of atenolol (1mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

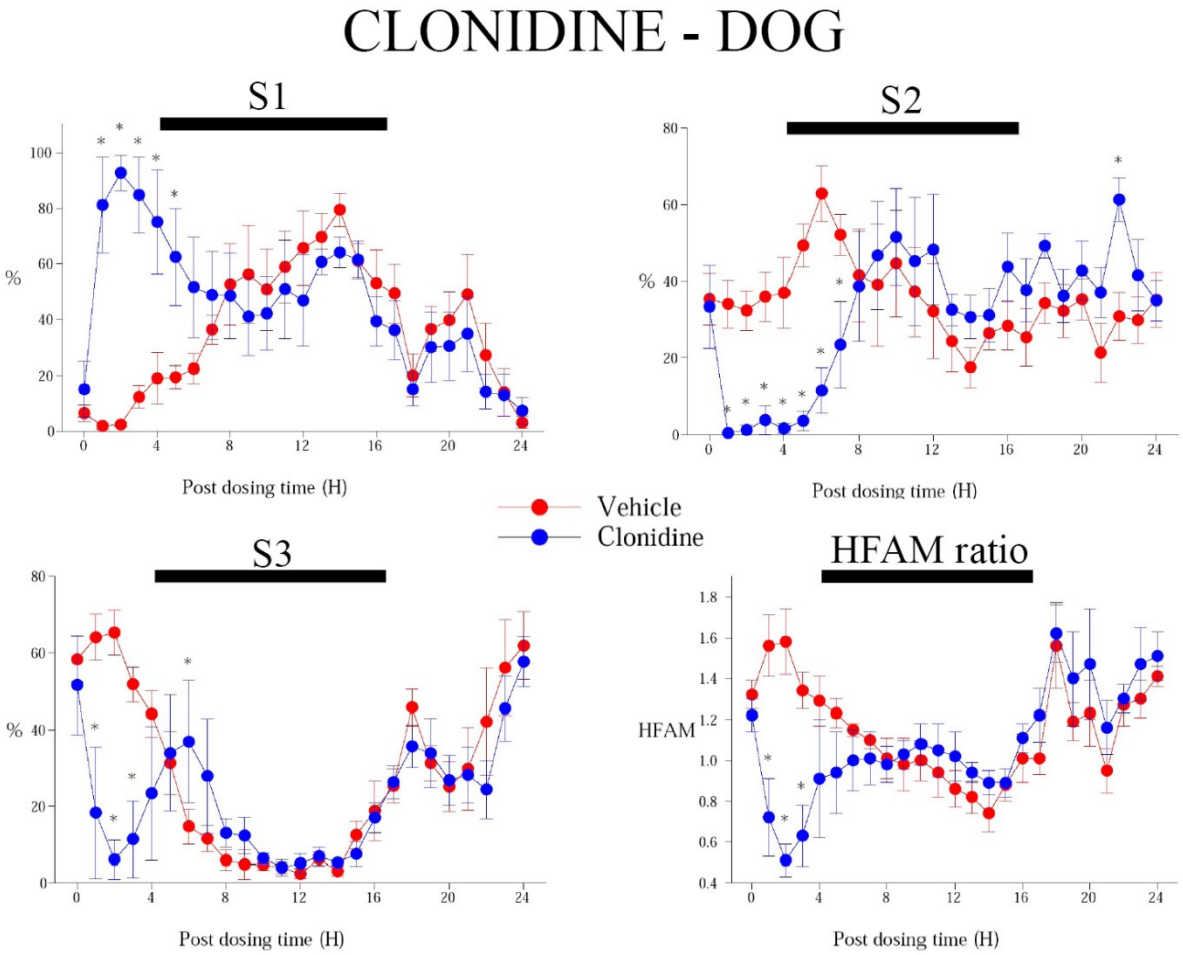

Figure 6. Effect of clonidine (0.1mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

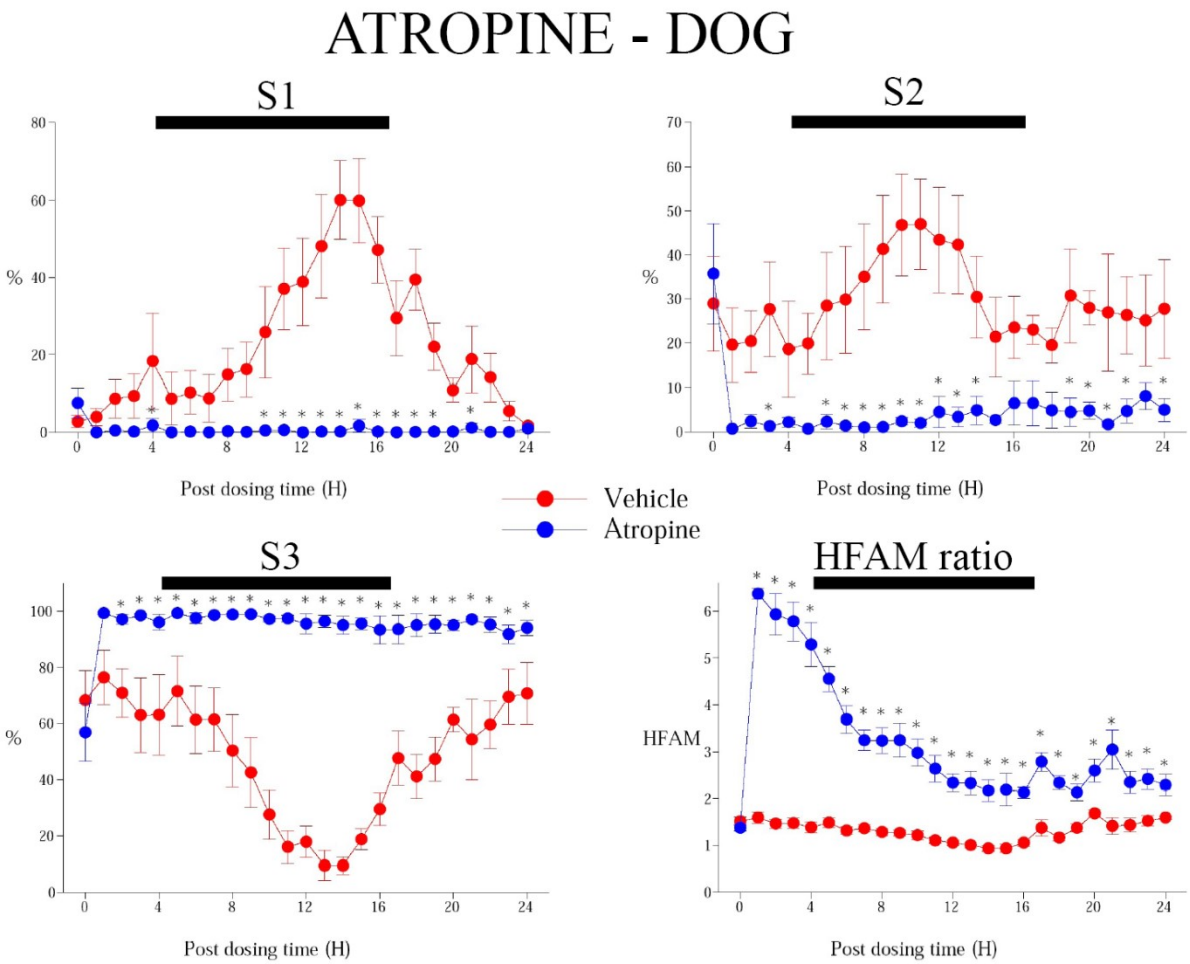

Figure 7. Effect of atropine methyl-nitrate (1 mg/kg, iv) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

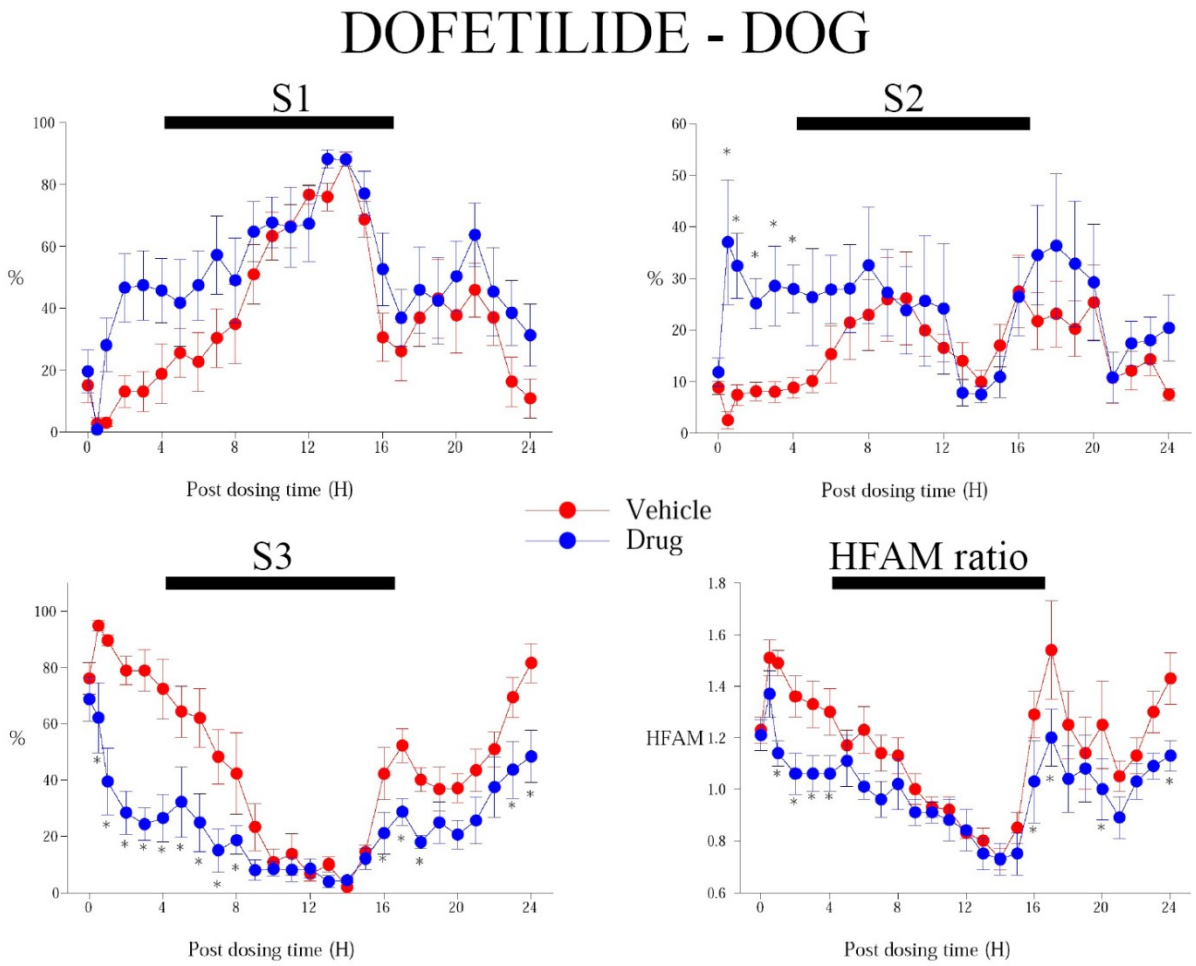

Figure 8. Effect of dofetilide (1 mg/kg, po) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

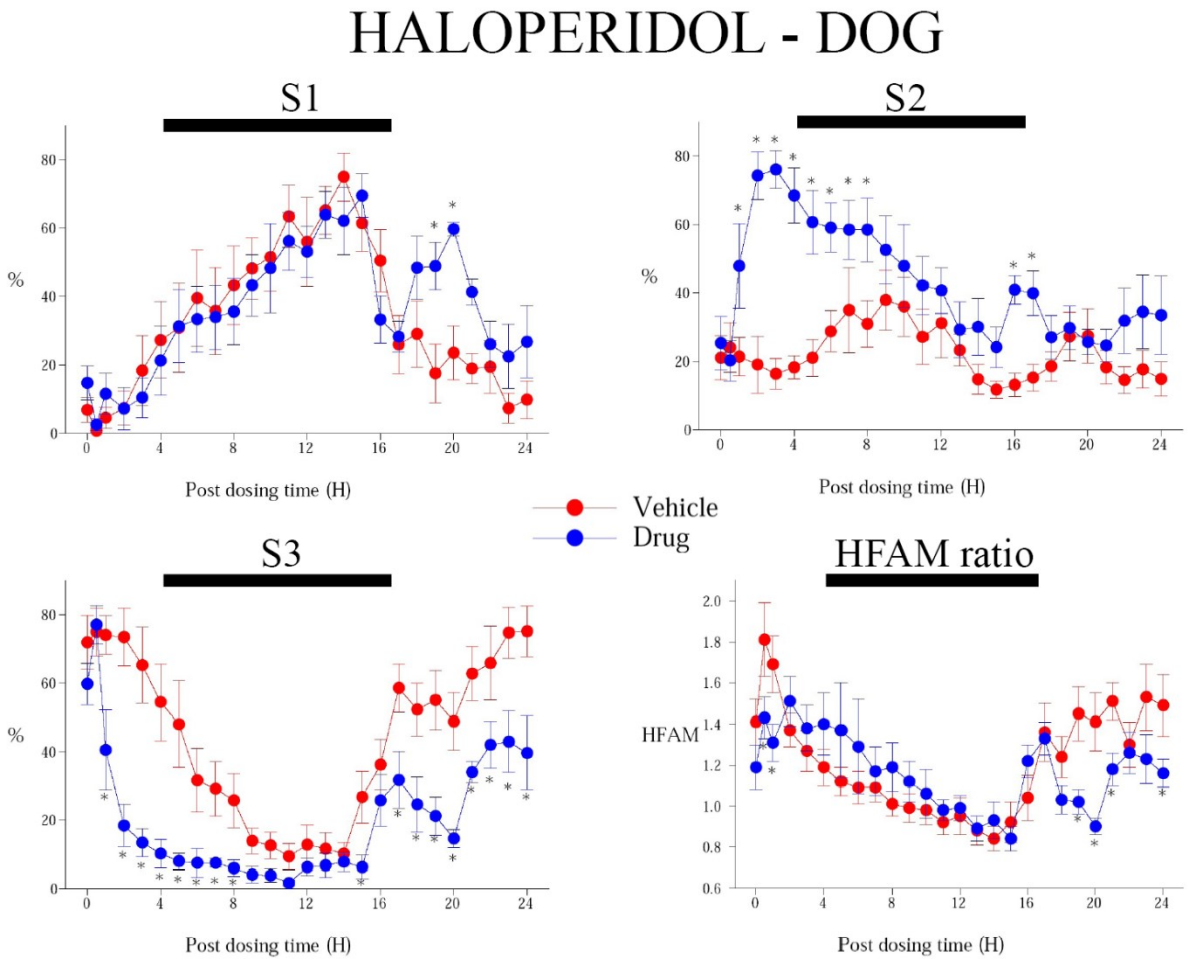

Figure 9. Effect of haloperidol (3 mg/kg, po) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

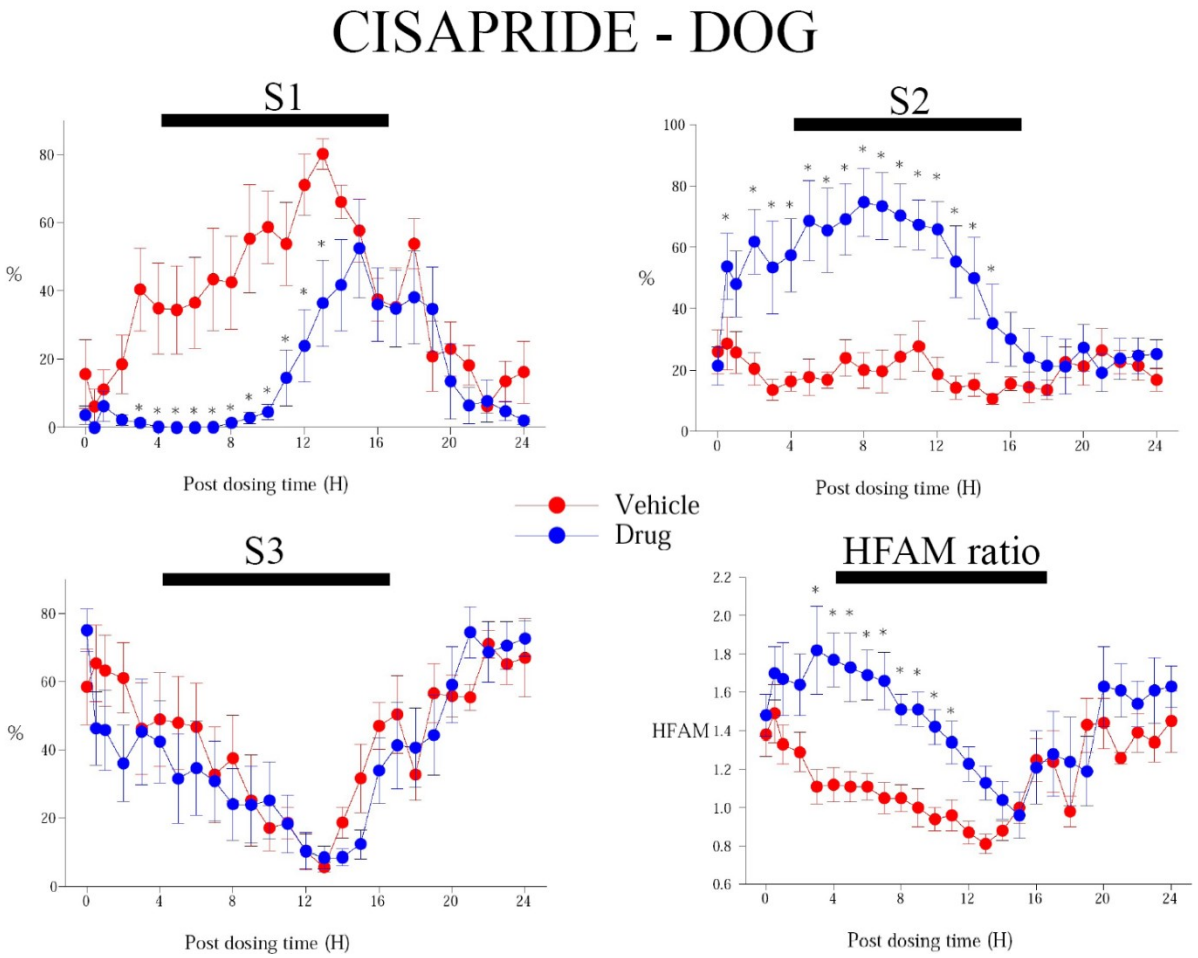

Figure 10. Effect of cisapride (6 mg/kg, po) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

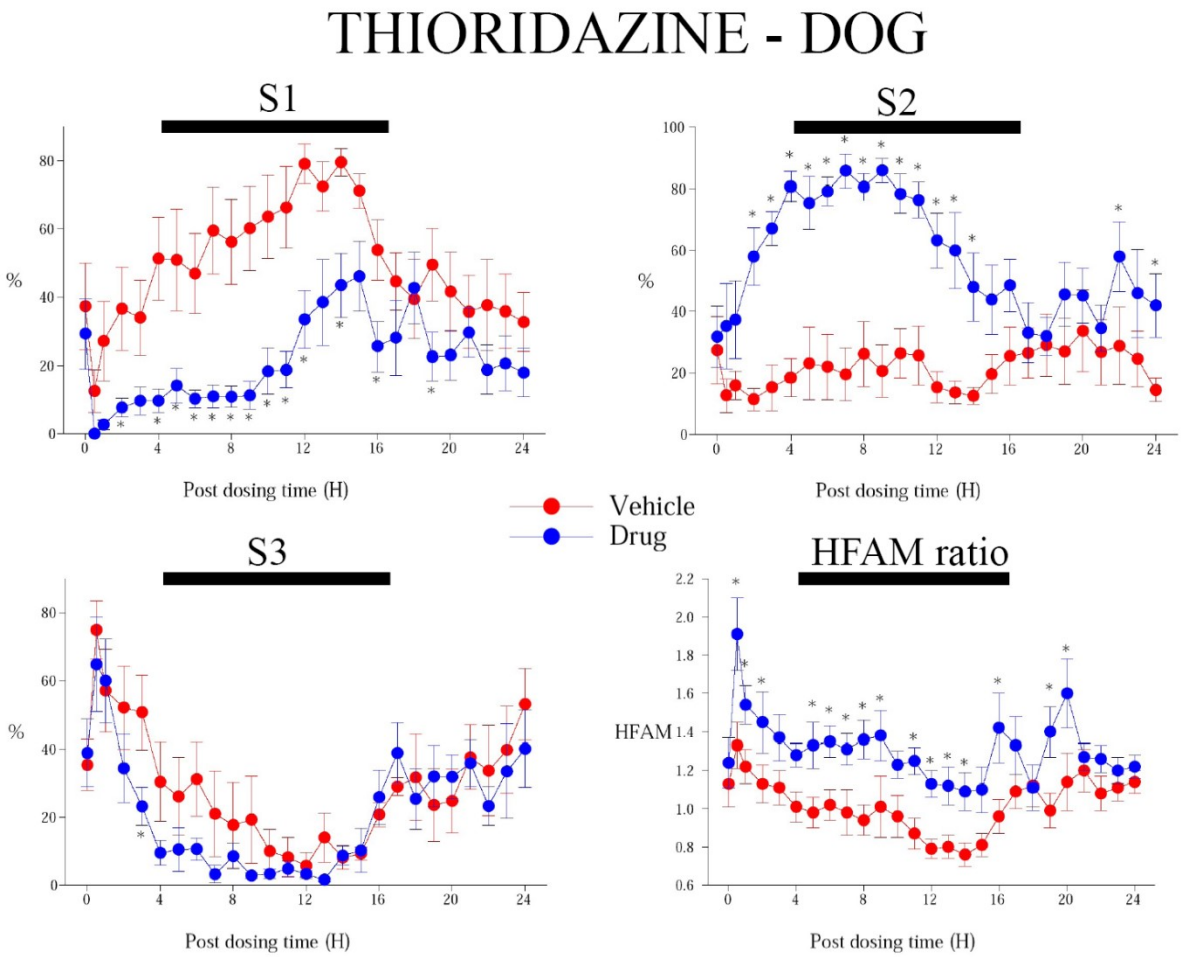

Figure 11. Proportions in % per hour. Effect of thioridazine (1.5 mg/kg, po) on S1, S2 and S3 oscillations and on the HFAM ratio in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Proportions in % per hour. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

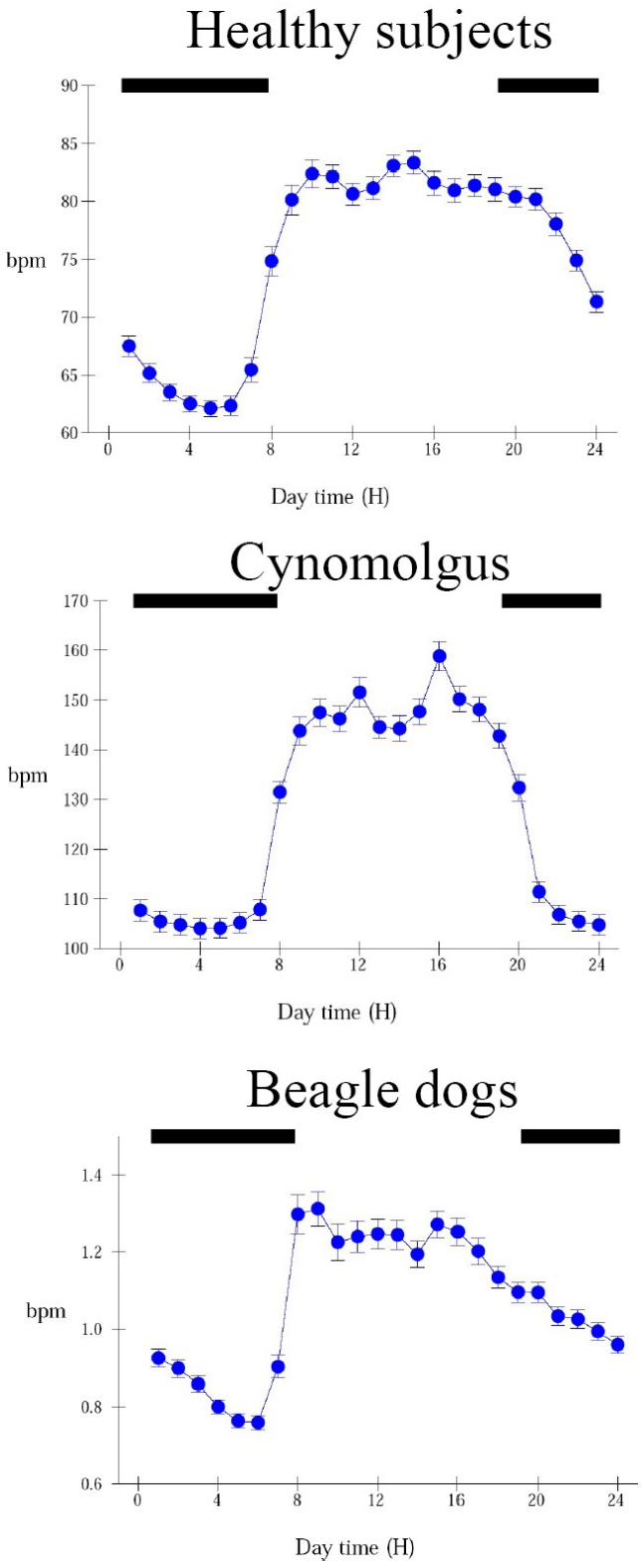

Figure 12. Circadian changes in heart rate in healthy subjects (n=200), cynomolgus monkeys (n=77) and beagle dogs (n=82). Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Data are presented as mean values ± SEM (n=6).

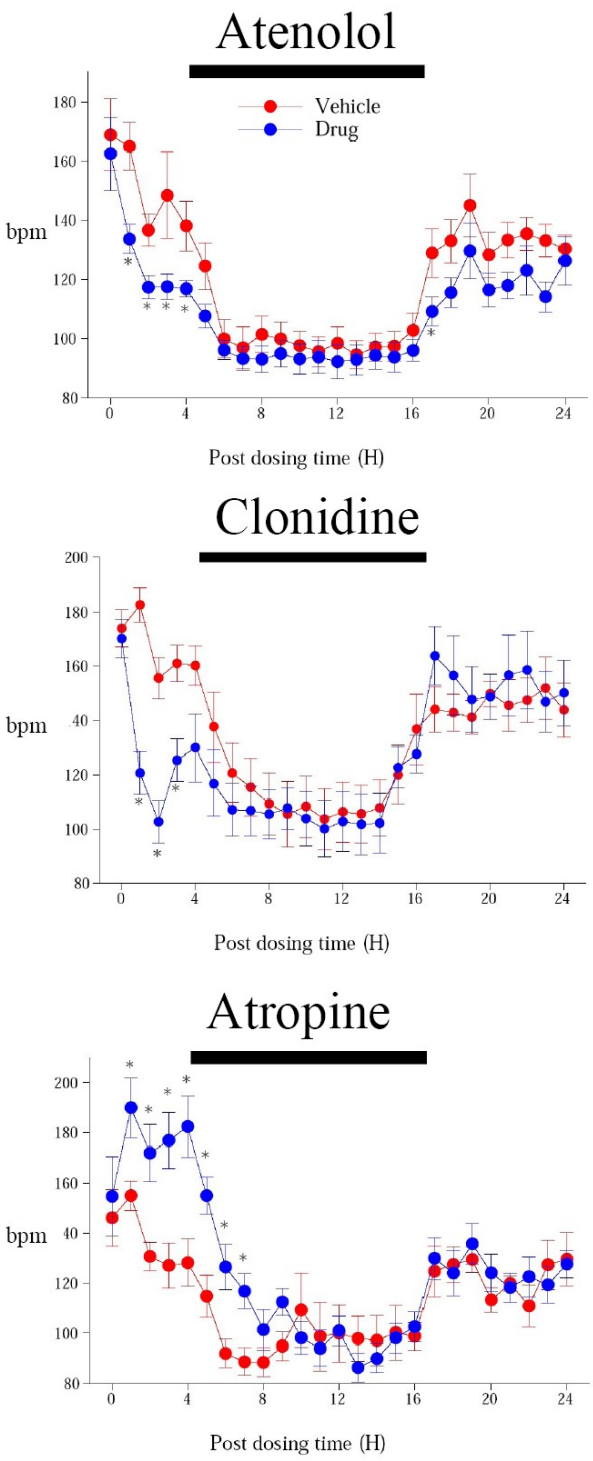

Figure 13. Effect of atenolol (1 mg/kg, iv), clonidine (0.1mg/kg, iv) and atropine sulphate (1 mg/kg, iv) on mean heart rate in cynomolgus monkeys. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

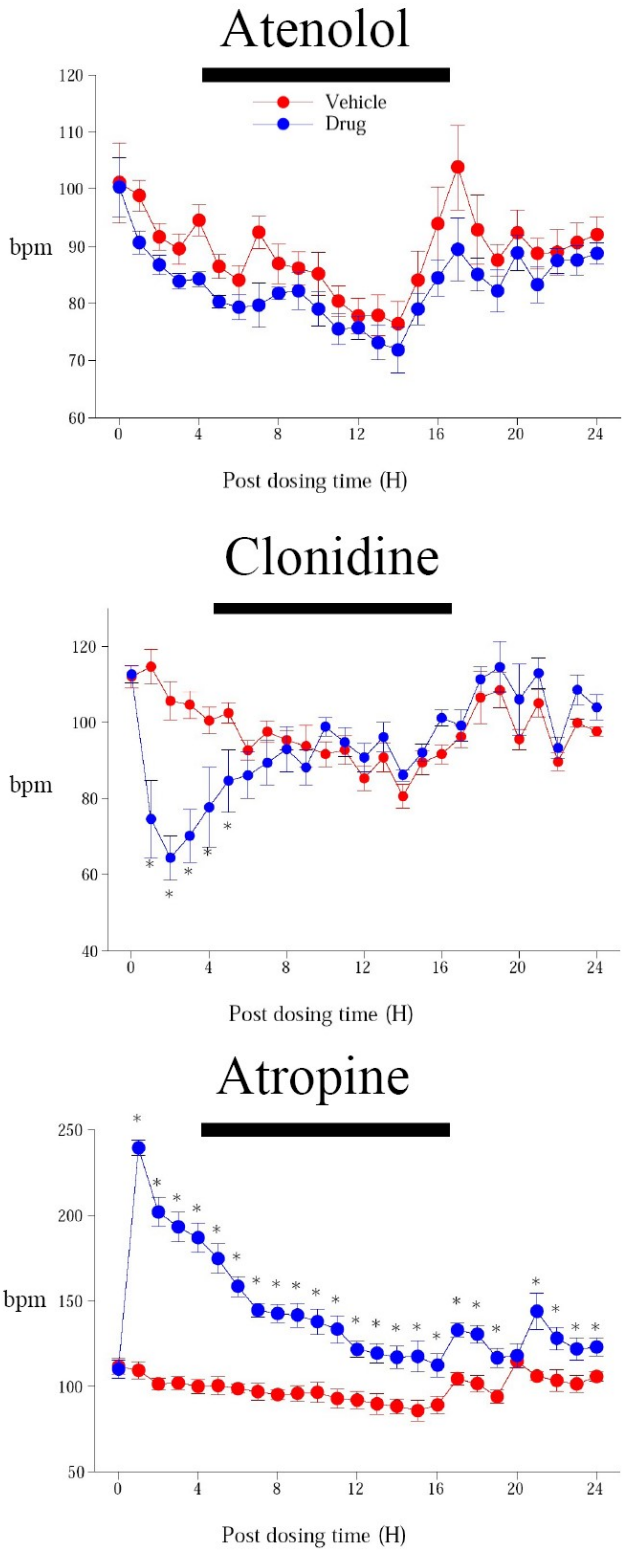

Figure 14. Effect of atenolol (1 mg/kg, iv), clonidine (0.1mg/kg, iv) and atropine methyl-nitrate (1 mg/kg, iv) on mean heart rate in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).

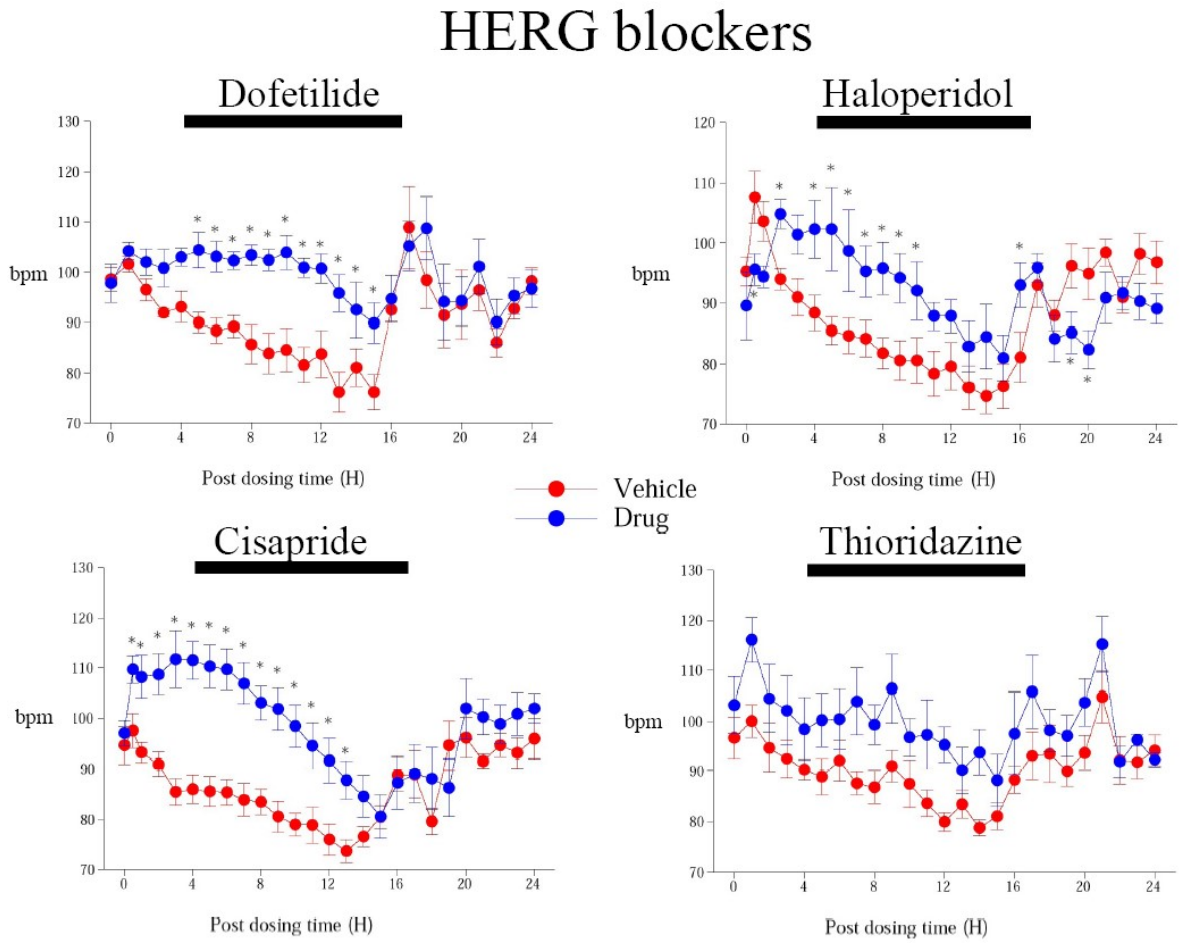

Figure 15. Effect of dofetilide (1 mg/kg, po), haloperidol (3 mg/kg, po), cisapride (6 mg/kg, po) and thioridazine (1.5 mg/kg, po) on mean heart rate in beagle dogs. Black line: Dark period of the 12-hour-light/12-hour-dark cycle. Data are presented as mean values ± SEM (n=6, *: P≤0.05, when compared to vehicle).